Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Description

Radioembolization (RE), also referred to as selective internal radiotherapy (SIRT), is the intra-arterial delivery of small beads (microspheres) impregnated with yttrium-90 via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumor preferentially to normal liver, as the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while normal liver is primarily perfused via the portal vein. RE has been proposed as a therapy for multiple types of primary and metastatic liver tumors.

Summary of Evidence

The available evidence for the use of radioembolization (RE) for the treatment of primary and metastatic liver tumors varies depending on the tumor type.

For the use of RE in the treatment of hepatocellular carcinoma (HCC), the evidence consists primarily of retrospective and prospective observational studies, with limited evidence from randomized controlled trials (RCTs). Observational studies suggest that RE has high response rates compared with historical controls. Two small pilot RCTs compared RE with alternative therapies for HCC, including transarterial chemoembolization (TACE) and TACE with drug-eluting beads, both of which demonstrated similar outcomes for RE. Evidence from observational studies demonstrates that RE can allow successful liver transplantation in certain patients. The available evidence, including clinical input, is sufficient to draw conclusions and to determine that outcomes are improved for the use of RE for the treatment of primary HCC that is unresectable and limited to the liver or as a bridge to liver transplantation.

For the use of RE in the treatment of hepatic metastases from neuroendocrine tumors, the evidence consists of one open-label phase 2 study, retrospective reviews and case series, some of which compare RE with other transarterial liver-directed therapies. This evidence suggests that RE has similar outcomes to standard therapies and historical controls for patients with neuroendocrine tumor-related symptoms or progression of liver tumor burden. There was support from clinical input for the use of RE for the treatment of hepatic metastases from neuroendocrine tumors. Therefore, the available evidence is sufficient to determine that RE is associated with improved outcomes for the treatment of hepatic metastases from neuroendocrine tumors.
A major cause of morbidity and mortality in patients with colorectal disease metastatic to the liver is liver failure, as this disease tends to progress to diffuse, liver-dominant involvement. For the use of RE in the treatment of unresectable metastases from colorectal carcinoma, the evidence consists of several small- to moderate-sized RCTs, prospective trials, and retrospective studies using a variety of comparators, along with systematic reviews of these studies. Although this evidence describes wide ranges of clinical response to therapy, there was strong support from clinical input for the use of RE for the treatment of hepatic metastases from colorectal cancer; the use of RE to decrease tumor bulk, and/or halt the time to tumor progression and liver failure, may lead to prolonged progression-free and overall survival in patients with no other treatment options (i.e., those with chemotherapy refractory liver-dominant disease). Other uses include palliation of symptoms from tumor bulk. Therefore, the available evidence is sufficient to determine that RE is associated with improved outcomes for the treatment of colorectal carcinoma liver metastases with liver-dominant disease.

For the use of RE for the treatment of intrahepatic cholangiocarcinoma, the evidence consists of retrospective and prospective observational studies, some of which compare RE with alternative therapies. Although no randomized trials are available, there is some suggestion that RE for primary intrahepatic cholangiocarcinoma has response rates similar to those seen with standard chemotherapy. RE may play a role for patients with unresectable tumors that are chemorefractory or unable to tolerate systemic chemotherapy. Clinical input in 2015 supported the use of RE for intrahepatic cholangiocarcinoma. Given the low likelihood of large-scale clinical trials for this rare tumor, the available evidence is sufficient to conclude that RE is associated with improved outcomes for patients with primary intrahepatic cholangiocarcinoma.

Similarly, for other tumors metastatic to the liver, including breast cancer and melanoma, the evidence consists of observational studies. In 2015, clinical input supported the use of RE for the treatment of liver-dominant metastases from breast cancer and melanoma in patients who are not candidates for or who have not responded to systemic therapies. Given the clinical input, the available evidence is sufficient to conclude that RE is associated with improved outcomes for patients with hepatic metastases from breast cancer and melanoma with liver-dominant disease.

**Policy**

Radioembolization may be considered **medically necessary** to treat primary hepatocellular carcinoma that is unresectable and limited to the liver (see Policy Guidelines).

Radioembolization may be considered **medically necessary** in primary hepatocellular carcinoma as a bridge to liver transplantation.

Radioembolization may be considered **medically necessary** to treat hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms.

Radioembolization may be considered **medically necessary** to treat unresectable hepatic metastases from colorectal carcinoma, melanoma (ocular or cutaneous), or breast cancer that are both progressive and diffuse, in patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies.

Radioembolization is considered **investigational** for all other hepatic metastases except as noted above.

Radioembolization may be considered **medically necessary** to treat primary intrahepatic cholangiocarcinoma in patients with unresectable tumors.

Radioembolization is considered **investigational** for all other indications not described above.
Policy Guidelines

In general, radioembolization is used for unresectable HCC that is greater than three cm.

There is little information about the safety or efficacy of repeated RE treatments or about the number of treatments that should be administered.

Radioembolization should be reserved for patients with adequate functional status (Eastern Cooperative Oncology Group [ECOG] Performance Status 0-2), adequate liver function and reserve, Child Pugh score A or B, and liver-dominant metastases.

Symptomatic disease from metastatic neuroendocrine tumors refers to symptoms related to excess hormone production.

Background

The use of external beam radiotherapy and the application of more advanced radiotherapy approaches (e.g., intensity-modulated radiotherapy) may be of limited use in patients with diffuse, multiple lesions due to the low tolerance of normal liver to radiation compared with the higher doses of radiation needed to kill the tumor.

Various nonsurgical ablative techniques have been investigated that seek to cure or palliate unresectable hepatic tumors by improving locoregional control. These techniques rely on extreme temperature changes (cryosurgery or radiofrequency ablation [RFA]), particle and wave physics (microwave or laser ablation), or arterial embolization therapy including chemoembolization, bland embolization, or RE.

RE, referred to as SIRT in older literature, is the intra-arterial delivery of small beads (microspheres) impregnated with yttrium-90 via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumor preferentially to normal liver, as the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while normal liver is primarily perfused via the portal vein. Yttrium-90 is a pure beta-emitter with a relatively limited effective range and short half-life that helps focus the radiation and minimize its spread. Candidates for RE are initially examined by hepatic angiogram to identify and map the hepatic arterial system. At that time, a mixture of technetium 99-labelled albumin particles is delivered via the hepatic artery to simulate microspheres. Single photon emission computed tomography imaging is used to detect possible shunting of the albumin particles into gastrointestinal or pulmonary vasculature.

Currently, two commercial forms of yttrium-90 microspheres are available: a glass sphere, TheraSphere® (manufactured by Nordion, Ontario, Canada, under license by BTG International) and a resin sphere, SIR-Spheres® (Sirtex Medical, Lake Forest, IL). Noncommercial forms are mostly used outside the United States. While the commercial products use the same radioisotope (yttrium-90) and have the same target dose (100 Gy), they differ in microsphere size profile, base material (i.e., resin vs. glass), and size of commercially available doses. The physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and dosimetry calculations. FDA granted premarket approval (PMA) of SIR-Spheres® for use in combination with 5-flouxuridine chemotherapy by hepatic arterial infusion (HAI) to treat unresectable hepatic metastases from CRC. In contrast, TheraSphere® was approved by humanitarian device exemption (HDE) for use as monotherapy to treat unresectable HCC. In January 2007, this HDE was expanded to include patients with HCC who have partial or branch portal vein thrombosis. For these reasons, results obtained with one product do not necessarily apply to other commercial (or noncommercial) products (see Regulatory Status section).

Unresectable Primary HCC

Most patients with HCC present with unresectable disease, and treatment options are limited secondary to the...
chemoresistance of HCC and the intolerance of normal liver parenchyma to tumoricidal radiation doses. Results of two RCTs have shown a survival benefit for TACE therapy compared with supportive care in patients with unresectable HCC.1, 2 In one study, patients were randomly assigned to TACE, transarterial embolization (TAE), or supportive care. One-year survival rates for TACE, TAE, and supportive care were 82%, 75%, and 63%, respectively, and two-year survival rates were 63%, 50%, and 27%, respectively. Targeted therapies have been investigated for HCC. For example, sorafenib was associated with improved OS in a randomized phase 3 trial with 602 patients.3

**Unresectable Intrahepatic Cholangiocarcinoma**

Cholangiocarcinomas are tumors that arise from the epithelium of the bile duct and are separated into intrahepatic and extrahepatic types. Intrahepatic cholangiocarcinomas appear in the hepatic parenchyma and are also known as peripheral cholangiocarcinomas. Resection is the only treatment with the potential for cure, and five-year survival rates have been in the range of 20% to 43%.4 Patients with unresectable disease may select among fluoropyrimidine-based or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation or best supportive care.

**Unresectable Metastatic CRC**

Fifty to sixty percent of patients with CRC will develop metastases, either synchronously or metachronously. Select patients with liver-only metastases that are surgically resectable can be cured, with some reports showing five-year survival rates exceeding 50%. Emphasis on treating these patients with potentially curable disease is on complete removal of all tumor with negative surgical margins. Most patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease. In patients with metastatic disease limited to the liver, preoperative chemotherapy is sometimes used in an attempt to downsize the metastases to convert the metastatic lesions to a resectable status (conversion chemotherapy).

In patients with unresectable disease that cannot be converted to resectable disease, the primary treatment goal is palliative, with survival benefit shown with both second- and third-line systemic chemotherapy.5 Recent advances in chemotherapy, including oxaliplatin, irinotecan, and targeted antibodies like cetuximab, have doubled the median survival in this population from less than one year to more than two years.5 Palliative chemotherapy by combined systemic and HAI may increase disease-free intervals for patients with unresectable hepatic metastases from CRC.

RFA has been shown to be inferior to resection in local recurrence rates and five-year OS and is generally reserved for patients with potentially resectable disease that cannot be completely resected due to patient comorbidities, location of metastases (i.e., adjacent to a major vessel), or an estimate of inadequate liver reserve following resection. RFA is generally recommended to be used with the goal of complete resection with curative intent.6 The role of local (liver-directed) therapy (including RE, chemoembolization, and conformal radiotherapy) in debulking unresectable metastatic disease remains controversial.6

**Unresectable Metastatic Neuroendocrine Tumors**

Neuroendocrine tumors are an uncommon, heterogeneous group of mostly slow-growing, hormone-secreting malignancies, with an average patient age of 60 years. Primary neuroendocrine tumors vary in location, but most are either carcinoids (which most commonly arise in the midgut) or pancreatic islet cells. Carcinoid tumors, particularly if they metastasize to the liver, can result in excessive vasoactive amine secretion including serotonin and are commonly associated with the carcinoid syndrome (diarrhea, flush, bronchoconstriction, right valvular heart failure).

Although they are considered to be indolent tumors, at the time of diagnosis, up to 75% of patients have liver metastases, and with metastases to the liver, five-year survival rates are less than 20%. Surgical resection of the metastases is considered the only curative option; however, less than 10% of patients are eligible for resection, as most patients have diffuse, multiple lesions.
Conventional therapy is largely considered to be palliative supportive care, to control, eradicate, or debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching. Therapies for unresectable metastatic neuroendocrine tumors include medical (somatostatin analogs like octreotide), systemic chemotherapy, ablation (radiofrequency or cryotherapy), TAE or TACE, or radiation. Although patients often achieve symptom relief with octreotide, the disease eventually becomes refractory, with a median duration of symptom relief of approximately 13 months, with no known effect on survival. Systemic chemotherapy for these tumors has shown modest response rates of limited duration, is better for pancreatic neuroendocrine tumors compared with carcinoids, and is frequently associated with significant toxicity. Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration and a survival benefit has not been demonstrated.  

Miscellaneous Metastatic Tumors

Small case reports have been published on the use of RE in many other types of cancer with hepatic metastases, including breast, melanoma, head, and neck (including parotid gland), pancreaticobiliary, anal, thymic, thyroid, endometrial, lung, kidney, gastric, small bowel, esophageal, ovarian, cervical, prostatic, bladder, and for sarcoma and lymphoma.

Regulatory Status

There are currently two forms of yttrium-90 microspheres approved by FDA. 

A glass sphere system, TheraSphere® (manufactured by Nordion, Ontario, Canada, under license by BTG International) was approved through the HDE process in 1999 for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic arterial catheters (H980006).

A resin sphere system, SIR-Spheres® (Sirtex Medical, Lake Forest, IL), was approved through the PMA process in 2002 for the treatment of inoperable CRC metastatic to the liver.

FDA product code: NAW.

Related Protocols

Cryosurgical Ablation of Primary or Metastatic Liver Tumors
Microwave Tumor Ablation
Radiofrequency Ablation of Primary or Metastatic Liver Tumors
Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.
References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


